SCIENCE

FEBRUARY 3, 1950

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VOLUME 111, NUMBER 2875

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

SCIENCE

Vol. 111 No. 2875 Friday, February 3, 1950

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Science, a weekly journal founded in 1880, is published each Friday by the American Association for the Advancement of Science at the Business Press, 10 McGovern Ave., Lancaster, Pa. Editorial and Advertising Offices, 1515 Massachusetts Ave., N.W., Washington 5, D. C. Telephone, Executive 6060. Cable address, SCIMAG, Washington, D. C. Entered as second-class matter at the Post Office at Lancaster, Pa., January 13, 1948, under the Act of March 3, 1879. Acceptance for mailing at the special rate postage provided for in the Act of February 28, 1925, embodied in Paragraph 4, Sec. 538, P.L. and R., authorized January 13, 1948.

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Health Hazards in Radiation Work

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THE CONNOTATION of the term *radiation hazard,* which has become common in the last decade, is limited almost entirely to dangers associated with ionizing radiations, and it is with this restricted concept of radiation hazards that the present discussion is concerned. Accordingly, the term *radiation,* unless obviously used in its broader sense, implies ionizing radiation. It is well to reflect in passing, however, that along with ionizing radiations one should also class as hazardous certain other radiations which, having been known much longer, have grown familiar and are generally considered to present no threat to man's well being. Radiant energy in the form of heat and light has definite biological effects, not all of which are either harmless or clearly understood. The disastrous effects of an increase in the sun's temperature beyond the relatively narrow range that is tolerable have received their share of speculative attention. Of more immediate importance is the possibility that as the result of exposure to excessive heat one may suffer severe or fatal burns. The effect of overexposure to sunshine is of no less significance, for there is unequivocal evidence that in addition to producing painful sunburn and even immediate death, such overexposure can induce skin cancer under certain conditions. On a purely statistical basis, the possibility that an individual will incur damage as a result of overexposure to radiation is very much greater in these latter instances than in the case of ionizing radiations.

The fact that ionizing radiations could produce injury first came directly to the attention of the medical profession when persons working with radiation began to develop definite abnormalities which could not be attributed clearly to other causes. The first examples of such abnormalities were noted within the year following Roentgen's original discovery of x-rays. It was observed, for example, that severe skin reactions and temporary or permanent baldness sometimes appeared after exposure to the rays. By the beginning of 1897, at least 23 cases of skin lesions from overexposure to x-rays had been reported in the literature, and the effects of the radiation on deeper tissues were becoming apparent. In July 1897, a note in a British publication, *Methodist Times* (*13*), referring to roentgen ray experiments on plants, included the prophetic comment, "It is of great importance that we should ascertain exactly what is the influence of these rays on living things, both plant and animals, for no doubt grave considerations of health are involved."

Types of Injurious Radiations

Before proceeding with a consideration of safety standards in radiation work, it is well to review briefly the nature of the radiations that constitute hazards. At the outset, it should be emphasized that all types of ionizing radiations produce similar biological effects —namely, cell destruction of some degree. Biologically speaking, x-rays, gamma rays, alpha and beta particles, and neutrons differ for the most part only in the distribution and the magnitude of the destruction produced.

X-rays are probably the most familiar of the ionizing radiations, and their use for diagnostic and therapeutic purposes is widespread. The properties of x-rays are very similar to those of visible light except that the wavelength is much shorter, so that x-rays penetrate many objects opaque to visible light. The use of x-rays in hospitals and industries constitutes the chief hazard from this type of radiation.

Protection in modern hospital radiology departments is as a rule entirely adequate to insure the safety of personnel responsible for routine diagnostic and therapeutic work. Obviously this is true only if there are no flagrant violations of accepted technique. In institutions equipped with very high voltage x-ray machines, the problems are increased considerably because of the greater penetrating power of the beam. In some cases, these high voltage machines have had to be housed entirely separately in order to avoid radiating the occupants of near-by rooms. Fluoroscopists may receive excessive irradiation, especially of the hands, which customarily enter the x-ray beam to palpate or manipulate the organs being examined. Leaded gloves and aprons afford good protection; however, the fingers of radiologists and others who have occasion to utilize the technique of fluoroscopy repeatedly over a period of years are likely to show some signs of radiation injury, as evidenced by changes in finger ridge detail.

Gamma rays are similar to x-rays, except that they have shorter wavelengths and are more penetrating. Formerly, these rays were observed only in association with the naturally occurring radioactive elements, of which radium is perhaps the best-known example. Now, however, they are also produced by high voltage x-ray machines, accelerators, and chain-reacting piles. Many of the more commonly employed artificially radioactive elements are also gamma-emitters. Potential exposure to gamma radiation is therefore widespread; however, the continuing use of radium in medicine still constitutes an important hazard.

The other ionizing radiations are particulate in nature and in this respect differ from x-rays and gamma rays. The particles of alpha rays are doubly charged helium atoms. These rays are strongly ionizing but only slightly penetrating. Once in the tissues, the radiations are highly effective in producing damage. Because of their poor powers of penetration, however, the slightest barrier will protect a worker from alpha rays. Certain isotopes of all elements heavier than lead are alpha-emitters. Of these, radium and its disintegration products and plutonium and polonium are probably the most commonly encountered, and the possibility that these may gain access to the body by ingestion, inhalation, or through an open wound constitutes the main hazard in this instance. After an alpha-emitting isotope has gained access to the body, a certain proportion of the element is more or less permanently deposited in some tissues, notably bone.

In the case of radium, for example, although the initial elimination following ingestion is rapid, permanent retention in humans has been found to vary between 0.1 percent and 10 percent of the intake, with an average of about 2 percent (*2*). In four human cases of chronic radium poisoning, the coefficients of elimination were found to be from 0.002 percent to 0.005 percent per day, a rate which would require approximately 45 years for the elimination of half the fixed radium present in the body—provided, of course, no further radium intake occurred (*3, 10, 11*). In such instances, the tissues are subjected to constant and highly damaging irradiation. The fact that there is often no efficient method for hastening the removal of deposited isotopes from the body enhances the significance of internal contamination in any work with radioactive isotopes.

Radiologists and technicians who work with radium also run the risk of overexposure to external gamma radiation. As in fluoroscopy, the hands usually receive the greatest dose; however, the total body irradiation is by no means negligible (*12*).

The particles of beta rays are electrons. They have greater penetrating power, but produce less ionization than alpha radiation. Almost all radioactive isotopes are beta-emitters and constitute one of the chief sources of potential exposure. Beta radiation also originates from the various accelerators, but the possibility of direct exposure in such instances is very slight. The prolific production of radioactive isotopes by the chain-reacting pile has made isotopes relatively easily available to many interested groups and the hazards associated with production, transportation, and utilization, as well as disposal of waste products, have increased proportionately. By strict regulation of shipping procedures and by limiting the distribution of isotopes to those institutions which have adequately trained personnel and monitoring equipment, it is hoped that the beta radiation hazard, despite its potential magnitude, will in reality remain small.

The seriousness of the hazard encountered in work involving any type of radioactive isotope is dependent in part on the half-life of the isotope under consideration. Other factors being equal, the longer the half-life, the greater the hazard. This relationship arises from the manner in which the customary unit for measuring radioactivity is defined, i.e., the *curie*, which is that amount of material undergoing the same number of disintegrations per second as a standard preparation of radium. The present value of the curie is 3.61×10^{10} disintegrations per second. Radioactive decay is a first-order process; hence the total quantity of radioactive element corresponding to a specified fraction of a curie increases directly with the half-life, as does the mean duration of potential exposure to the radiations given off. In the case of C^{14}, for example, the estimated half-life of approximately 6,000 years makes work with this isotope more hazardous than would be expected on the basis of the weak beta radiation given off during decay.

Neutrons are uncharged particles which have a mass approximately equal to that of the hydrogen atom. They are produced when atomic nuclei are disrupted by bombardment with alpha particles, protons, deuterons, electrons, neutrons, or gamma rays. By virtue of their zero charge, neutrons have great penetrating power. Formerly the chief neutron hazard was associated with the operation of cyclotrons and to a lesser extent with investigations utilizing such neutron sources as radium-beryllium mixtures. The chain-reacting pile is now an important source of potential neutron exposure, and the prevention of such exposure was an important consideration in designing appropriate protection. It is to be expected that neutron hazards will continue to increase with the constantly growing interest in both the theoretical and applied aspects of nuclear physics, and the associated construction of more and bigger and better particle accelerators in universities and research institutions. Impaired vision as a result of work with neutrons has

become of particular interest recently, since several nuclear physicists have developed cataracts (*1*). The production of cataracts by neutron irradiation has also been observed in experimental animals (*6*). All available evidence indicates that gross overexposure is necessary to produce this effect.

Recognizing the Hazard

Since the mere existence of hazards is not a legitimate barrier to progress in any field, the alternative of minimizing the dangers associated with hazardous work had to be accepted and developed. This has involved both the development of criteria for safe working conditions and the establishment and maintenance of such conditions.

The evolution of criteria of safe working conditions is an interesting story. In spite of the early observations that certain adverse effects might follow exposure to x-rays, the obvious implication that harmful effects might result from working with the radiation was not immediately recognized, and many pioneers in radiology suffered severe injuries before the existence of the hazard was acknowledged. This was particularly true of the hands as reflected in the high incidence of cancer of the hands among early roentgenologists.

Utilization of x-rays to treat cancers and other conditions made it possible to study changes in relatively large numbers of persons under fairly well-controlled conditions, and it was soon observed that the radiation was beneficial to the patient only insofar as it was detrimental to the abnormal tissue. In the early days, the problem of therapy was complicated by the fact that there was no convenient or widely accepted method of measuring the dosage administered. The first patients were also treated without benefit of the years of accumulated statistics which now constitute an important tool of the radiation therapist. As a result of these factors, many patients received x-ray doses considerably in excess of the therapeutic amount, and showed clear evidence of damage to normal tissues as well as, in many instances, a marked generalized adverse response to the treatment. Since these early days there has been progressive improvement in the measurement of radiation dosage, and today the techniques are quite satisfactory for therapeutic purposes.

The harmful effects of radiations from radium were not recognized so promptly as in the case of x-rays, and Madame Curie herself died as a result of radium poisoning in 1934 (*4*). This was 32 years after the original purification of radium chloride, and approximately 35 years after the discovery of polonium. The classical tragedy of radium poisoning among radium dial painters in New Jersey during the 1920's clearly established the position of radium poisoning as an important industrial health hazard. In this instance, the workers, mostly young women, ingested highly toxic amounts of radium as a result of the practice of pointing their paint brushes with their lips. The development of severe fatal anemia or bone cancer several years after the exposure was supposed to have ceased demonstrated a major difference between prolonged exposure to small amounts of radiation and prolonged exposure to many other toxic substances (*8*).

Once the hazardous nature of the early radiation work was clearly recognized, evidence of radiation damage was deliberately sought in occupations involving potential exposure to ionizing radiations. In the late 1930's, the increased incidence of chronic lung diseases, including cancer of the lung, among miners in the Joachimsthal uranium mines received considerable attention and was eventually found to be directly related to the radiation received (*9*). A great deal of attention also came to be focused on changes induced in radiologists and others by the small amounts of radiation which they received repeatedly during the course of their work.

Accumulated observations clearly indicated that any effect radiation had on normal tissues was essentially harmful, and that radiation produced more or less damage, depending on the ability of the tissue under consideration to withstand the initial insult and subsequently to repair itself by normal processes. There have been several flurries of interest over the so-called stimulating effects of radiation, but these have invariably turned out to be misinterpretations, usually of recovery phases following radiation damage. Inestimable harm has resulted from ignorant exploitation of the supposedly stimulating effects of radiation. The sale of water containing radioactive material and the therapeutic use of x-rays and radioactive substances by untrained persons have been responsible for many serious or fatal radiation injuries.

As already indicated, much of the data originally used in estimating a safe dose was obtained from patients receiving radiation therapy, and from routine observations on radiologists and technicians. In the case of the latter group, the method of determining the safe dose often consisted of determining how much radiation was received per day under conditions where precautions were considered to be adequate. That daily dose was then considered to be safe if, after a relatively long period of time, there were no observable signs of injury in persons so exposed. There are several difficulties inherent in such a procedure, most of which are readily apparent. First, unless the observations designed to detect injury cover many organ systems, there is a good possibility that existing damage will not be detected because it is not sought in the right manner, or is not considered at all. This

difficulty encompasses almost all of the latent changes which may follow prolonged or frequent exposures to very small doses of radiation. Further, as it became apparent that lower and lower doses could produce definite changes, it became equally apparent that there was no justification for risking the health of personnel on the assumption that absence of observed changes implied the absence of injury.

The growing recognition of the harmful effects of radiation on normal tissues resulted in studies designed to determine how much radiation could be received without incurring detectable damage. This amount has come to be known as the tolerance dose. Although there are many differences of opinion as to the exact interpretation of the term, the concept of a tolerance dose is concerned chiefly with repeated exposures to small amounts of radiation over a long period of time. The basis for determining the tolerance dose did not change materially for many years, and most revisions in safety standards consisted of successive reductions in previously accepted permissible exposure levels. Neutron tolerances, for the most part, have been based on the relative effectiveness of neutrons and x-rays or gamma rays in producing certain biological effects. In the case of radium the permissible exposure level (i.e., the permissible amount of radium deposited in the body) was established on the basis of cases of radium intoxication in industry. Gradually, however, a more conservative attitude has been adopted. The issue is no longer how much radiation may be received without apparent ill effects, but how little radiation an organism may receive and still show definite changes, either immediately or remotely.

Recent revisions of tolerance doses have been based largely on the results of long term animal experiments designed to provide detailed information relative to the damage produced by prolonged exposures near the tolerance range. Tolerance levels that have been established for the various isotopes have been determined by similar experiments, taking into account the importance of the metabolism of the substances in question, aside from their radioactivity.

It is clear, after reviewing the development of the present concept of safe working conditions, that one of the great obstacles was the failure to consider the possible existence of radiation hazards. But now, the evaluation of such hazards is one of the most important aspects of health protection in radiation work.

Effects on the Worker

The determination of safe working conditions in any specific instance requires information in three separate categories: namely, information relative to the types and intensities of radiations involved, a knowledge of the nature of the exposures, and an appreciation of the biological effects of these radiations. The various kinds of radiation and the more common instances in which they may be encountered have already been discussed briefly. The intensities of radiation vary greatly, depending upon the nature of the work, and must be determined by careful measurements in each situation. To this end, considerable effort has been expended since the discovery of x-rays and radioactivity, and the development of improved instruments and films for the quantitative estimation of radiation has become an increasingly important aspect of health protection. As a result of the advances in this field, satisfactory quantitative estimation of radiation is now possible in most instances. It is desirable, however, that the physical monitoring devices be more sensitive than any radiation-sensitive process in human physiology, and this has not been achieved in all cases.

Exact determination of the type and intensity of radiation encountered in a given instance is often difficult or impossible because of the mixture of radiations present. This is especially true in the case of cyclotrons and other accelerators, and the chain-reacting piles. Further complications occur in certain of these because the relative proportions of the radiations vary and are not always predictable. These uncertainties render the interpretation of the biological effects which follow exposure to such radiation extremely tenuous and make the definition of safe working conditions somewhat arbitrary, with the result that poor agreement often exists relative to the permissible exposure.

With regard to the nature of the exposure, it has already been pointed out that frequently repeated exposures to relatively low doses constitute the greatest hazard in contemporary radiation work. The problem of a limited number of exposures to relatively large doses of radiation is of more immediate concern in the case of patients receiving radiation therapy or individuals exposed to radiation from military explosions; however, the possibility of occasional accidental gross overexposure in experimental work cannot be entirely overlooked. The health protection program in the various atomic energy installations has been successful to a degree almost totally unprecedented, and there have been remarkably few instances of definite overexposure. A recent official tally indicates that only fifteen such incidents have occurred in the six years since the program was undertaken. Only two of the injuries were fatal, and eleven of the remaining thirteen individuals involved either were unhurt or apparently recovered completely.

An appreciation of the biological effects of radiation plays an extremely important role both in the recognition of radiation hazards and in the definition

of safe working conditions. Despite the fact that details of the biological effects have not yet been completely unraveled, certain general aspects of these effects are now well recognized. Studies on animals deliberately exposed to radiation indicate that all tissues do not respond similarly to a given amount of radiation. This variation includes the amount of radiation which the various tissues can withstand without detectable damage, the rate at which they appear to respond to doses which produce damage, and the rate and extent of recovery from damage. Cell division in the skin of the mouse, for example, can be entirely inhibited for a short period following exposure to 35 roentgen units of x-rays, whereas cell division in the adrenal gland of the same animal is only 50 percent inhibited by the same exposure (*14*). Skin, white blood cells, bone marrow, reproductive cells, and the cells lining the intestine have long been known to respond readily to relatively small doses of radiation. Adult red blood cells, bone, and nerves, on the other hand, tend to be more or less resistant. Further differences in the susceptibility to radiation damage can be demonstrated in cells of slightly different lineage within a given tissue, as well as among various constituents of individual cells. In experimental animals it is possible to observe all tissues for gross, microscopic, and chemical changes after irradiation. In man it has been necessary to rely on less comprehensive studies in determining the relative radiation sensitivity of various tissues.

A fortunate circumstance exists in the fact that the blood cells and the tissues from which they originate are among the most radiosensitive of all tissues, both in man and in animals. Blood can also be obtained easily and frequently, with a minimum of inconvenience and no danger to the individual. For these reasons, hematological changes have come to be regarded as one of the important methods of detecting radiation damage, and as more detailed studies are undertaken it appears that hematological changes may be far more sensitive indicators of radiation damage than was formerly supposed on the basis of purely routine observations. In the case of the mixture of radiations originating from the cyclotron, for example, it is possible under certain conditions to observe definite indications of a response on the part of the white blood cells in instances where the radiation received is well within the accepted limit according to routine monitoring devices. Blood findings are particularly important in total body irradiation. When exposure is limited to a single part, as for example the hand, a generalized response may not be elicited and the value of hematological examinations is probably limited. Studies of changes in finger ridge detail, however, are of considerable importance in such cases.

In addition to indicating variability in the response of the several tissues to irradiation, animal experiments also indicate that under certain conditions there may be delayed manifestations of damage from a long series of frequent exposures. Specifically, these late results are premature aging, the indication of tumors, decreased fertility, and genetic changes, as well as the previously mentioned induction of cataracts. These effects have all been observed in animals following continued exposures at levels corresponding to doses somewhat above the accepted safe tolerances for man. The induction of tumors and cataracts, however, are the only delayed effects, that have been observed in man, and these appear to follow only relatively gross overexposures. There is a great deal of speculation and equivocation relative to the possibility that decreased fertility and genetic changes will be observed in man after a sufficient number of years or after a sufficient number of generations, as the case may be. In the absence of sufficient data on humans, however, it has been necessary to rely entirely on the results of animal experiments in predicting the occurrence of such changes. On the basis of experimental evidence it appears, in general, that the greater the exposure, the greater will be the number of gametes with altered genes or chromosomes. Many authorities feel that *any* amount of ionizing radiation may produce hereditable changes and that in any individual the effects are cumulative, not only throughout the life of the individual but throughout the entire life of the germ plasm (*5*). Mutations induced by exposure to ionizing radiation are thought to be of the same type as those which occur naturally, and either chromosome or gene mutations may occur. Most mutations are recessive and their effects on subsequent generations are deleterious, resulting in developmental anomalies, marked interference with early development so that the embryo does not survive, or a decreased fertility. In general, gene mutations tend to produce anatomical and physiological anomalies, whereas chromosome mutations tend to manifest themselves as decreased fertility. In either case, large numbers of the population must be affected if the induced changes are to be significant in subsequent generations.

Not all the experimental evidence supports the postulate that extremely low doses of radiation increase the incidence of mutations. In a recent extensive investigation of several years' duration, various species of animals were exposed daily to radiation in amounts near the tolerance range. Breeding experiments were carried out as a part of the study and the incidence of mutations was found not to be increased above the normal, even though other harmful effects were produced in these groups (*7*).

It has been suggested that even if a slight increase

in the production of mutations should occur as the result of exposure, the end result would be altered by such factors as a tendency towards decreased fertility in the offspring of irradiated parents and the tendency for many mutations to be lethal or to shorten the life span and reproductive period of the individual. In other words, natural selection would tend to be against mutants. The possibility that irradiation might occasionally induce the reversal of a previous mutation has also been considered as a mechanism for minimizing the genetic effects of radiation.

The interesting controversy relative to the ability of prolonged exposure to small doses of radiation to induce changes is far from a satisfactory settlement, and the possibility that radiation-induced genetic changes may occur in radiation workers continues to be an important consideration in defining safe levels of exposure.

The limitations of experimental studies utilizing animals can never be entirely removed, even with perfectly accurate measurements, for man is not exactly comparable in anatomy or physiology to any of the experimental animals. The contributions from animal experiments, however, have been extremely important, and the data so obtained have done much to light the way towards an understanding of the biological effects of radiation, without which adequate protection of individuals working with ionizing radiations would have been almost impossible. If the antivivisectionists were to have their way, all of the information now available would be based on human misfortune—even, no doubt, involving some of them. It is doubtful, however, that even an antivivisectionist could suppose that information obtained under such unfortunate and poorly controlled conditions would be very useful to the problem at hand.

Safety Measures

Since it is impossible to obtain all the information necessary to define absolutely safe conditions for man, the accepted standards at any given time will be in the nature of approximations, and it is to be expected that revisions will be repeatedly proposed. The uncertainty involved in designing safety standards, however, has been offset to a large extent by the general attitude of conservatism regarding health aspects of radiation work, and the excellent health records of the many groups working with powerful sources of radiation during the war years prove that it is entirely possible to minimize radiation hazards if sufficient effort is made.

In order to achieve conditions where hazards are minimal, it is necessary not only to recognize the hazards and define safe working conditions, but also to maintain these conditions. The latter point is critically important, and it involves training personnel in the necessary techniques, as well as educating them or at least impressing them with the importance of the imposed regulations. It is also necessary to provide adequate physical facilities for protection and monitoring, and to enforce the necessary regulations. The philosophy concerning work with ionizing radiations should in many ways be similar to that concerning work with disease-producing bacteria and viruses. In both cases, the agent in question is harmless until it invades the privacy of the individual, and the basic rule governing protective techniques is to keep the agents rigidly confined to their own environments. In radiation work, this involves keeping a certain amount of distance between the worker and the source of radiation. This distance must be large relative to the ability of the specific radiations in question to traverse it; however, it may be physically great or small, depending upon the medium of which it is constituted. In most cases the physical distance can be shortened by interposing between the source and the individual a substance which readily absorbs the radiation. This procedure, known as shielding, is one of the most important methods of providing physical protection.

No amount of shielding, however, can replace the individual worker's constant vigilance, for it is only by virtue of individual reliability in this respect that hazards can be kept at a minimum. To this end it is vitally important that, regardless of formal education, the individual be well schooled in the techniques of whatever operations he performs, and that he realize the importance of observing the rules and regulations which apply to his own sphere of activity. In some instances the highly trained professional personnel concerned with research in nuclear physics and radiation chemistry did their initial work prior to the accumulaton of knowledge pertaining to the health hazards involved. In other cases investigators have not kept informed about the biological effects of radiation. Having suffered no apparent harm, they tend to be lax in the personal application of health safety regulations and may be as much in need of education as the most unschooled worker.

Because health hazards in radiation work have been kept so low, the medical profession in general has not been confronted to any great extent with the problem of treating radiation injuries. This lack of experience does not represent any sizable addition to the radiation health hazard, however, for although the biological effects of exposure to radiation may be complex, they are not unique. Treatment will generally be an issue only in fairly gross overexposures, which constitute but a single aspect of the over-all problem. It is generally agreed that there is not,

nor is there likely to be, any single specific remedy for radiation injury, to correspond, for example, to penicillin for some infections.

The physiological phenomena following total body exposure consist of a complicated sequence of changes which are more or less interrelated and interdependent. Not all of these are well understood. Treatment may be expected to modify the immediate outcome of radiation injury insofar as it can modify the more devastating changes. Some of these, such as burns, dehydration, anemia, and the diffuse infections which follow marked decreases in the number of white blood cells, can be treated by well-known and accepted methods. Treatment for other aspects of severe radiation injury, where the nature of the basic abnormality is more obscure, is the subject of a great deal of research being carried on at the present time. For example, the problem of treatment of the marked bleeding tendency which develops as a result of single gross overexposures is being approached from many diverse directions by various investigators. In all instances, treatment is aimed toward supporting life and bolstering the body's defenses until natural reparative processes can become active, and it is fair to say that the over-all prospect of treating the more immediate manifestations of acute radiation injury is by no means hopeless. In the case of protracted exposures to doses near the tolerance level, the main considerations are somewhat different. Because of the preponderance of latent changes at these levels of exposure, the problem of treatment is almost entirely one of prevention. This, as has been shown, is entirely feasible. As more adequate treatment of acute radiation injury is developed, the relative importance of latent changes in those instances, too, may increase markedly, and those latent effects which had previously been observed only in experimental animals might become the most commonly observed effects of acute radiation injury in man.

Radiation has gained a permanent foothold in modern science and industry, and society is presently struggling to learn to live with it. Health protection of radiation workers has been remarkably successful in atomic energy installations. It has been possible, for the most part, to keep exposures not only at tolerance levels but considerably below them, and the general health of the workers has been better than that in most other industries. The attitude of alarm which has been so commonly associated with the idea of radiation work can safely be discarded, provided it is replaced by one of healthy respect for protective rules. It remains to be seen whether or not the knowledge, skill, and caution thus far accumulated will be applied on a wider scale now that work with radiation is becoming increasingly common throughout this country and the world.

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The Mechanism of the Heat Inactivation of Pepsin[1]

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PROTEIN DENATURATIONS, including enzyme inactivations, have usually been considered to be first-order unimolecular processes (*1, 7*), although in a number of investigations marked deviations from first-order behavior have been observed (*2, 8*). The work has usually been carried out by calculating first-order rate coefficients and examining their constancy with respect to time. This procedure suffers from a disadvantage arising from the fact that impurities and products generated in a reaction may interfere with the progress of the reaction. In order to avoid this possibility we have recently made a study of the heat inactivation of pepsin in which we have measured the initial rate as a function of both initial concentration and temperature.

The results have been somewhat unusual, and appear to go some way towards explaining the anomalous and apparently inconsistent results obtained by previous workers. If the initial rate, v_0, of a reaction is related to the initial concentration, c_0, by the power law

$$v_0 = k\, c_0^n, \qquad (1)$$

where k and n are constants, a plot of log v_0 against log c_0 will give a straight line, the slope of which is

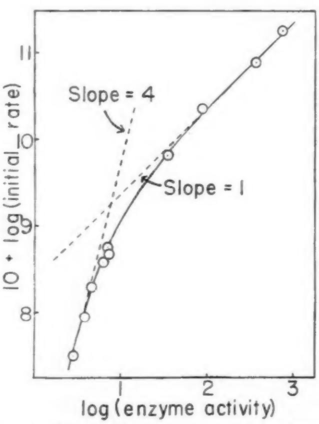

Fig. 1. Plot of log (initial rate) vs. log (initial enzyme activity) for the inactivation of pepsin at pH 4.83 and a temperature of 57.8° C.

[1] This work was carried out in part under contract N9ONR-91100 with the Office of Naval Research, Biological Sciences Division, Biochemistry Branch.

the index n. When this procedure was applied to our data, the curve shown in Fig. 1 was obtained. It is evident that in fact the index n is not constant, but that it varies with the initial concentration. Over a certain range of high concentrations n is very close to unity (that is, the reaction is of the first order), but as the concentration is decreased, the value of n increases, and finally it reaches a value of about 5. It is clear from this analysis that in the low concentration region the usual first-order coefficients will not be constant but will decrease markedly with increasing time. On the other hand, in the high concentration region good first-order constants are to be expected, and we have confirmed with our own data that this is the case. It would therefore appear that those workers, such as Arrhenius (*1*) and Northrop (*3*), who obtained good first-order constants, were working in the region of high concentration; drifting constants, on the other hand, may be due to the fact that the work was done in the low concentration region (*2, 8*).

TABLE 1

Reaction Orders and Activation Energies Corresponding to Various Pepsin Concentrations

% Pepsin by weight	Activity*	E_{exp}	n
0.004	2.90	147.0 ± 10	5.0
0.006	4.60	115.0 ± 3	3.0
0.008	6.20	109.0 ± 2	2.4
0.011	7.30	97.0 ± 2	2.1
0.050	25.9	80.0 ± 12	1.5
0.50	392	56.2 ± 0.5	1.0
4.00	2465	62.0 ± 10	1.0

* Expressed as meq. tyrosine per ml liberated from 4.0 ml of standard hemoglobin solution by 1.0 ml enzyme solution at 25.0° C and pH 1.9.

Some evidence as to the reason for this variation in apparent order with concentration is provided by the results of a study of the temperature dependence of the initial reaction rates. These were found to obey the Arrhenius law, but the resulting activation energy was influenced very markedly by the initial concentration; some values are included in Table 1, which gives also the order with respect to concentration corresponding to each enzyme concentration. The variation of activation energy with enzyme concentration is represented in Fig. 2.

The very considerable reduction in energy of activa-

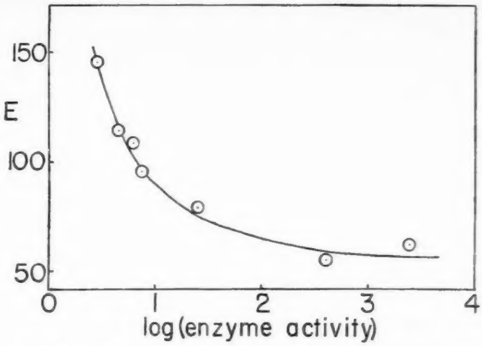

FIG. 2. Variation of activation energy E with enzyme activity for the inactivation of pepsin at pH 4.83.

tion with increasing concentration implies the existence of enormously strong repulsive forces acting between the pepsin molecules in solution. As a result of these, the protein molecules pass into states of higher and higher potential energy as the concentration increases, and consequently there is a diminution in the activation energy that it is necessary for them to acquire prior to becoming deactivated. We have confirmed that the magnitude of these repulsive forces is of the same order as that of those revealed by the osmotic pressure experiments of Scatchard *et al.* (*4, 5, 6*) on albumin. These forces are presumed to be electrostatic in nature, and to be due in part to the zwitterion character of the enzyme and in part to the presence of adsorbed ions.

The existence of these repulsive forces explains the variation in reaction rates with the initial concentration, since the process of activation is seen to be a cooperative phenomenon involving the presence of a group of protein molecules surrounding each protein molecule. At low concentrations the reduction in activation energy will be very sensitive to enzyme concentration, and the apparent order of the reaction will therefore be high; at sufficiently high concentrations, however, a saturation point will be reached, and the number of activated molecules will then be in proportion only to the first power of the enzyme concentration.

On the basis of the mechanism referred to above, it can be shown that the initial rate v_0 is related to the initial enzyme concentration c_0 by the approximate expression

$$v_0 = \frac{k_0 K c_0^n}{nKc_0^{n-1} + c_{H^+}^5} \tag{2}$$

where c_{H^+} is the hydrogen ion concentration, K is the equilibrium constant for complex formation, and k_0 is the rate constant for the deactivation of the enzyme in the complex. The value of n is approximately 5. At low concentrations of enzyme, $c_{H^+}^5 \gg nKc_0^{n-1}$, so that the initial rate is

$$v_0 = \frac{k_0 K}{c_{H^+}^5} c_0^n \tag{3}$$

and the reaction is of the nth (approximately fifth) order. At high concentrations, on the other hand, $nKc_0^{n-1} \gg c_{H^+}^5$, so that the rate is

$$v_0 = \frac{k_0}{n} c_0; \tag{4}$$

the reaction is then of the first order. We have confirmed that the mechanism explains not only the variation of initial rates with initial enzyme concentration but also the change of concentration of active enzyme with time in an individual rate measurement.

A paper presenting full experimental details and a quantitative treatment of the data will shortly be submitted for publication in the *Journal of the American Chemical Society*.

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Technical Papers

Absorption of Radioactive Zirconium and Niobium[1] by Plant Roots from Soils and Its Theoretical Significance

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In the last few years certain by-products of atomic fission have been made available for studying the mechanisms of ion uptake by plants and soils. In particular, a mixture of radioactive zirconium (Zr^{95}) and niobium (Nb^{95}) has been used by Sengupta (*5*) to study ion exchange between colloidal materials. This carrier-free mixture is received as the oxalate in the form of a complex which can be destroyed by the action of hydrogen peroxide in strong sulfuric acid. A product is obtained which is adsorbed very easily by clay and soil. Once adsorbed, the Zr and Nb are held very tenaciously and resist leaching by many reagents. For instance, dilute HCl and H_2SO_4 and up to 1*N* acetic acid fail to remove any of the adsorbed radioactive ions. Some organic acids are more efficient and their relative efficacy is illustrated by the data in Table 1. The relations indicated have been used by Tompkins *et al.* (*6*) as a means of separating several by-products of atomic fission by adsorption on cation exchange Amberlite, followed by leaching with various reagents. With this technique they leached out Zr and Nb, using 0.5% oxalic acid and 5% citric acid. In their opinion the successful leaching agents were those capable of forming complexes with these ions. It will be noted that at least five of the organic acids listed in Table 1 have been found to occur in plant tissues (*7*).

TABLE 1

RADIOACTIVE ZR AND NB REMOVED FROM YOLO SOIL BY VARIOUS LEACHING REAGENTS

Acid reagent	5 g Soil with an activity of 780 counts per minute leached with 100 ml of each solution. Radioactivity data from Geiger counter.							
	Normality of acid							
	.001		.01		0.1		1.0	
	Initial pH	cpm*	Initial pH	cpm	Initial pH	cpm	Initial pH	cpm
HCl	3.1	0	2.2	0	1.2	0	0.3	21
H_2SO_4 ...	3.1	0	2.2	0	1.3	5	0.5	35
Acetic ...	3.9	0	3.5	0	3.0	0	2.4	0
Oxalic ..	3.4	4	2.4	49	1.6	226	0.9	209
Citric ...	3.6	15	3.0	55	2.4	143	1.9	281
Lactic ...	3.6	1	3.0	4	2.4	35	1.8	221
Malic ...	3.6	8	3.0	57	2.5	128	2.0	137
Tartaric .	3.6	5	2.9	16	2.3	38	1.7	125

* Counts per minute.

Radioactive Zr and Nb were added to 900 g of Yolo soil and carrots were grown in this medium for 8 weeks. Control plants were grown in the same type of soil without Zr and Nb. The radioactivity measured in the plants at the end of the growth period is given in Table 2. These results confirm the observations of Jacobson and Overstreet (*1*), who found a high activity in roots and a weak activity in the shoots. There is no doubt that plants can assimilate Zr and Nb from soils.

Two main theories have been advanced to account for the mechanism of release of adsorbed ions by plant roots: the soil solution theory and the contact theory.

TABLE 2

RADIOACTIVITY OF ASHED CARROT TISSUES GROWN ON YOLO SOIL CONTAINING ZR^{95} AND NB^{95} AS MEASURED ON GEIGER COUNTER

Sample	Dry wt in g	Radioactivity cpm/g	Remarks on apparent contamination with radioactive soil
Soil	900	212	....
Leaves			
Active	3.4	26	None
Control	3.9	0	None
Fibrous Roots			
Active	1.3	106	Considerable
Control	1.4	0	None
Peeled Tap Root			
Active	1.8	0	None
Control	1.5	0	None
Tap Root Peelings			
Active	0.6	52	Slight
Control	0.6	0	None

The original version of the soil solution theory postulated that roots absorb ions present in the liquid phase of a soil system. The solvent action of water was held responsible for the transfer of ions from the unavailable solid phase to the available liquid phase. Later, the theory was modified to assign a role to respiratory carbonic acid excreted by roots into the soil solution. The H^+ in solution was exchanged for cations adsorbed on soil colloids, and these ions, now part of the soil solution, became available to plant roots. This mechanism does not require direct action of roots on soil colloids.

On the other hand, the contact theory of Jenny and Overstreet (*3*), while recognizing the existence of absorption from the soil solution, holds that many aspects of mineral absorption by plants growing in soils can be better explained by assuming direct transfer of ions from the soil colloid to the plant root also behaving as a col-

[1] Formerly known as columbium (Cb) before revision by the International Union of Pure and Applied Chemistry in September, 1949.

loidal particle. This mechanism by-passes the soil solution and postulates that hydrogen ions on the roots exchange directly for cations on the clay. The theory for cation exchange by contact is supported by theoretical considerations (*4*). A detailed account of both theories discussed briefly here was given recently by Jenny (*2*).

One difficulty in appraising these two mechanisms arises from the fact that ions exist in both the liquid phase, or soil solution, and in the solid phase, or soil colloid. From the data already presented, the possibility was considered that it might be possible to identify from which of the two phases the plants absorbed Zr and Nb. This prospect was explored experimentally in the following way. Five-gram samples of soil containing radioactive Zr and Nb with an activity comparable to that in which the plants were grown, were leached with a liter of each of the following solutions: Hoagland's solution in equilibrium with atmospheric CO_2, giving a pH of 5.0, and a similar solution saturated with CO_2, giving a pH of 3.9. Distilled water, under the same two CO_2 pressures, was also used as a leaching agent. Of the two leaching agents, Hoagland's solution was considered the more reasonable facsimile of what is understood by a soil solution. The use of CO_2 is an attempt to simulate the respiratory excretion of roots.

The leachings were evaporated to dryness and measured for activity on the Geiger counter. No activity was detected with any of the leaching solutions. From this it was concluded that no Zr and Nb were present in the soil solution and therefore the CO_2-soil solution theory was inadequate to explain the uptake of these radioactive substances by plants from soils.

However, from the leaching experiment with organic acids (Table 1) it is entirely within the realm of possibility that a soil solution theory incorporating as an important feature the excretion of organic acids by plant roots could very nicely explain the absorption of Zr and Nb. Such a theory might conceivably account for the uptake from soils of such ions as iron made available by complex formation with the same organic acids as were used in our leaching test. It is common practice in the water culture of plants to supply iron in the form of citrate or tartrate. So the organic acid theory offers a possible explanation, even though it has not been advanced very seriously as a mechanism for ion uptake. For instance, a recent review of organic acids in plants (*7*) considers their role as intermediates in respiration, as agents in the maintenance of cation-anion balance, and as participants in protein metabolism, but no mention is made of their possible excretion by roots in connection with ion availability.

Of course, it is not strictly necessary that plants themselves excrete organic acids, inasmuch as microorganisms in soils could perform this function just as well, to their mutual advantage. The biological excretion of organic acids has been demonstrated (*8*) and their function in increasing the availability of phosphate and potassium in soils has already been considered (*9*). Obviously, the possibilities of organic acids require serious consideration and investigation in relation to ion availability.

Another mechanism for explaining these results is offered by the contact theory. According to this idea, it is not necessary to have ions in solution in order for plants to absorb them. All that is required for an exchange of ions is the intermingling of the electric double layers between two colloidal particles. In this connection, some interesting results were obtained by Sengupta (*5*). He was able to remove Zr^{95} and Nb^{95} from clay by synthetic cation exchange resins such as Amberlite IR-100. This behavior would be analogous to the activity of a root acting in accordance with the contact exchange concept.

It is concluded that insofar as the absorption of radioactive Zr and Nb is concerned, the CO_2-soil solution theory does not offer a satisfactory explanation. The only possible mechanisms are offered by the contact theory or by a soil solution theory postulating the excretion of organic acids by plant roots or microorganisms growing in the same environment.

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New Method for Studying Electrical Orientation and Relaxation Effects in Aqueous Colloids: Preliminary Results with Tobacco Mosaic Virus

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Various investigators have observed the double refraction effects produced by the application of sinusoidal electric fields to suspensions of anisometric colloidal particles. Lauffer (*3*) studied by a visual method the birefringence produced in aqueous tobacco mosaic virus (TMV) solutions by 60-cycle sinusoidal fields. Mueller (*4*) and Norton (*5*) observed in bentonite aquasols birefringence which varied in magnitude and sign with the frequency of the applied sinusoidal voltage and the concentration of the sol. Although the phenomena are similar to the Kerr effect (*2*), a number of interesting anomalies have been reported which suggest the existence of orienting mechanisms other than those due to permanent or induced dipoles.

It seems clear that data obtained with sinusoidal fields

are difficult or impossible to interpret where different kinds of orientation may occur during a single cycle. Heating and electrophoretic effects are troublesome, particularly with biological materials. The apparatus described here utilizes an electronic switching circuit capable of producing pulses of alternate polarity[1] as shown in Fig. 1A, to minimize heating and polarization effects, and square waves (Fig. 1B), for certain experiments described below.

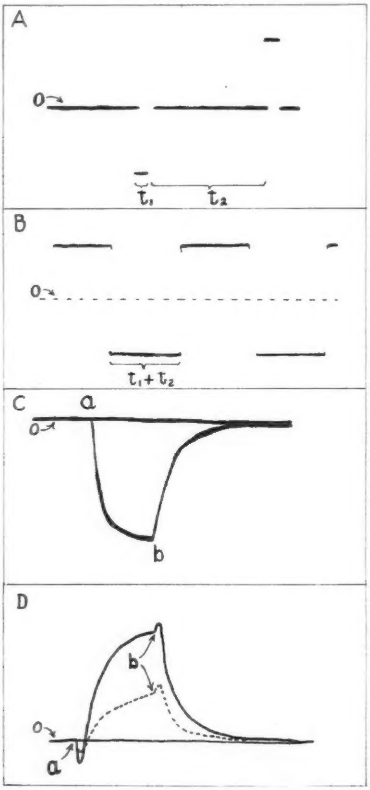

FIG. 1. Oscillograms of (A) pulses and (B) square waves generated across the cell by electronic switching circuit. In our experiments, $t_2 = 9t_1$; $t_1 = 3$, 0.3, or 0.03 msec. Rise time in all cases was one μsec. (C) The photosignal from 0.073% TMV solution. Linear sweep; sweep time = 10 msec; 238 v/cm pulse applied at *a* and removed at *b*, 3 msec later; applied voltage zero otherwise. (D) The same as (C) but with 1.4% TMV (solid curve) and 2.75% TMV (dashed curve). The relaxation is exponential in (C) but not in (D).

In the optical systems employed previously, the electric field was applied transversely to a cell containing the solution between crossed nicols oriented at 45° to the field, and an increase in light intensity was produced by birefringence of either sign. In the present apparatus, a $\lambda/4$ plate is interposed between the cell and the analyzing nicol, which is rotated slightly from the crossed position, with the result that light intensity increases when birefringence is positive, but decreases when it is negative. The transmitted light beam is focused upon an electron-multiplier phototube. A d-c wide band-pass amplifier converts photocurrent variations into vertical deflections of an oscilloscope beam, which is synchronized with the applied pulses for photography of the build-up and decay of the birefringence. The rectangular cell, $10 \times 5 \times 2.5$ mm, contains two bright platinum plane electrodes.

Because of random fluctuations in the photocurrent due to stray light transmitted by the crossed nicols, and the function relating the signal strength to the angle between the directions of polarization and of the analyzer, the maximum sensitivity (signal-to-noise ratio) is realized for small values of double refraction, other factors constant, when the analyzer is rotated from the crossed position by an angle α_m given by the equation

$$\sin\alpha_m \approx (I_s/I_o)^{\frac{1}{4}}, \tag{1}$$

where I_s is the stray light intensity and I_o is the total intensity. This ratio was determined experimentally for our optical system and gave $\alpha_m \approx 10°$. The sensitivity achieved in this way was shown to be greater than any sensitivity achievable without the $\lambda/4$ plate.

For any setting α, the relation between the change in light intensity ΔI and the optical retardation δ, in radians, of the ray vibrating along the electric field was found to be:

$$\Delta I = I_o \left[\frac{(2 \sin \alpha + \delta \cos \alpha)^2}{(4+\delta)^2} - \sin^2\alpha\right]. \tag{2}$$

For $\alpha = 10°$ and small values of δ, in which we are primarily interested, this reduces to:

$$\delta = 5.85 \frac{\Delta I}{I_o}. \tag{3}$$

By suitably calibrating the amplifier and oscilloscope and adjusting the photomultiplier current to a predetermined level, values of $\Delta I/I_o$ are obtained. This procedure compensates for any variations in the light source (a battery-operated tungsten lamp) or electron-multiplier sensitivity. Values of the optical retardation for the mean wavelength of the useful light are calculated from the above equations.

Fig. 1C shows an oscillogram typical of the results obtained with dilute TMV solutions.[2] Alternate positive and negative pulses separated from each other by a long period at zero potential (Fig. 1A) were applied to the electrodes of the cell, while the amplified photocurrent was introduced to the vertical plates of the oscilloscope. It can be seen that both the onset and removal of the voltage pulse are followed by an apparently exponential rise or fall of the birefringence of the solution. The time constant of the exponential curves is 0.6 msec, with the birefringence decaying to zero after the removal of the pulse. Since the photograph was a time exposure covering many pulses, it can be seen that the effect of

[1] This apparatus was developed before the authors became aware of the work of Benoit (*1*), who obtained pulses by means of a motor-driven interrupter.

[2] We are indebted to Dr. Howard Schachman of the Virus Laboratory for a purified sample of tobacco mosaic virus.

both positive and negative pulses is exactly the same. The birefringence in both cases is positive, i.e., the slow ray has its electric vector oriented parallel to the impressed electric field. Concentrations as low as 0.03% behaved similarly.

In Fig. 1D are sketched two of the curves observed with more concentrated virus solutions for a 3-msec pulse. The birefringence varies with time in a complex manner, first becoming slightly positive, then decreasing to zero

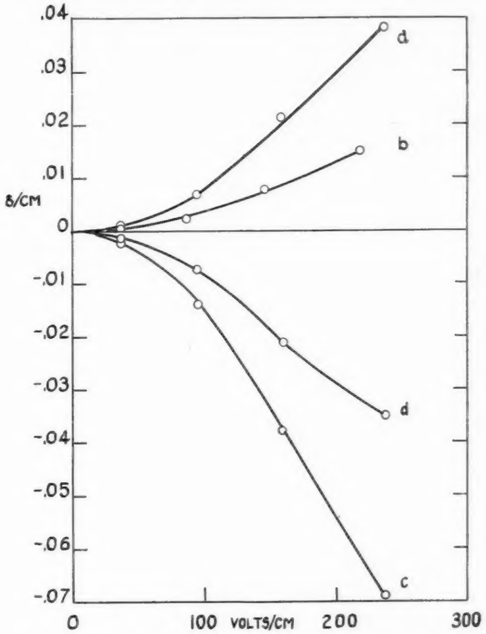

FIG. 2. Peak values of optical retardation in radians per centimeter of solution versus applied field strength: (a) 0.073% TMV, 1.5×10^{-4}M buffer; (b) 0.073% TMV, 1.0×10^{-3}M buffer; (c) 1.4% TMV, 1.5×10^{-4}M buffer; (d) 2.75% TMV, 1.5×10^{-4}M buffer.

and becoming negative, and finally becoming slightly more negative after the field is removed and before decaying to zero. The build-up and decay do not follow exponential curves and occur somewhat more slowly than in dilute solutions.

Employing 3-msec pulses, the peak values of birefringence were determined as a function of field strength for solutions of various virus and buffer concentrations. In all experiments a phosphate buffer, pH = 7, was used. Data are shown in Fig. 2.

If it is assumed that the rotations of the rodlike virus particles may be characterized by a rotational diffusion constant, D, a quantitative expression may be obtained for the time constant of the exponential decay. In this case the Brownian motion of the particles should follow the diffusion equation (*6*):

$$\frac{1}{D}\frac{\partial f}{\partial t} = \frac{1}{\sin\theta}\frac{\partial}{\partial\theta}\left[\sin\theta\left(\frac{\partial f}{\partial\theta} - \frac{Mf}{kT}\right)\right], \qquad (4)$$

where f is the distribution density of rods with respect to θ, the angle between the electric field and the axis of the rod, t is the time, M is the torque caused by the field, and k and T have their usual meanings. When the field is zero, corresponding to the relaxation between pulses in our experiments, M is zero and the solution of the equation is found by standard methods to be

$$f = a + bP_1(\cos\theta)e^{-2Dt} + cP_2(\cos\theta)e^{-6Dt} + \ldots, \qquad (5)$$

where the $P_n(\cos\theta)$ are the Legendre polynomials and a, b, and c are constants. Further investigation shows that the first term of this series that contributes to the polarization tensor characterizing the double refraction is the one involving $P_2(\cos\theta)$. Hence the double refraction is exponential in time, with a time constant of $1/6D$, unless higher order terms are unexpectedly important. Now using the formula of Perrin (*6*), simplified for $a \gg b$:

$$D = \frac{3kT}{16\pi\eta a^3}\left(-1 + 2\ ln\ \frac{2a}{b}\right), \qquad (6)$$

where $2a$ is the length of the particles and $2b$ is the diameter (here assumed to be 2800 A and 150 A respectively), one may calculate that the time constant should be 0.3 msec, compared with 0.6 observed. The disagreement is somewhat larger than would be expected.

The length of the particles calculated from the relaxation time, assuming $a/b = 19$, is 3660 A.

It is of considerable interest to determine the nature of the mechanism causing the birefringence. Four possibilities by which the particles may be oriented with respect to the electric field have been considered: (1) permanent dipoles, (2) induced dipoles, (3) viscous drag of the surrounding medium on particles moving by electrophoresis, and (4) distortion of the ionic atmosphere surrounding the particles.

If permanent dipoles were responsible for the observed orientation in dilute solutions one would expect the anomalous Kerr effect discovered by Raman and Sirkar (*7*), i.e., a decrease of δ with increase of frequency. Our calculations, based on equation 4, show that this effect would be very evident with square waves (Fig. 1B) at frequencies of the order of the reciprocal of the observed decay time constant. Experiments, however, showed that the peak birefringence remained constant within experimental error as the frequency of applied square waves was increased well beyond this point. This has led us to discount permanent dipole orientation as the mechanism responsible for the positive birefringence of dilute solutions. An attempt to treat the phenomena on the basis of a torque arising from translational electrophoretic motion of the anisometric particles in a viscous medium fails because of the well-known tendency of anisometric bodies consistently to orient themselves *across* the direction of motion.

It has been shown (*8*) that the torque on a dielectric ellipsoid within a dielectric medium will be in a direction to orient the ellipsoid along the applied electric field, whether the dielectric constant of the medium is greater or less than that of the ellipsoid. Thus, induced dipoles would give positive birefringence, as observed with dilute solutions. Since the induced dipoles reverse their directions when the field is reversed, the torque remains un-

changed and the birefringence with square waves should be equal to the steady state value with an equivalent steady field, and this is consistent with our observations. Because the conductivity of the dispersing medium will affect the ionic atmosphere and the electric field in the vicinity of a particle, a change of birefringence with buffer concentration is to be expected. The observed result, a decrease in birefringence with increasing buffer concentration, is illustrated in Fig. 2, curves a and b. The complex nature and reversal of sign of the birefringence at higher concentrations (curve c) might be due to interactions between the particles and their ionic atmospheres.

Whatever may be the orienting mechanisms involved, it is clear that the birefringence and its decay are very sensitive to the size and shape of the particles. For this reason, the method shows promise of application in aggregation studies and other investigations in which the size of large colloidal particles is important.

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The Induction of Resistance to 4-Amino-N^{10}-Methyl-Pteroylglutamic Acid in a Strain of Transmitted Mouse Leukemia[1]

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It has been shown previously (*2*, *3*) that there is a marked prolongation of the survival time of mice inoculated with transplanted leukemia Ak 4 when they are treated with 3 mg/kg of 4-amino-N^{10}-methyl-pteroylglutamic acid[2] (*6*) three times weekly to a total of ten doses. Even when treatment is continued until death, however, the mice eventually die of leukemia between the 28th and 40th day. In view of the ultimate failure of therapy observed with this and closely related substances in many clinical trials in acute leukemia, the mechanism of this eventual lack of response in mouse leukemia was deemed worthy of further investigation.

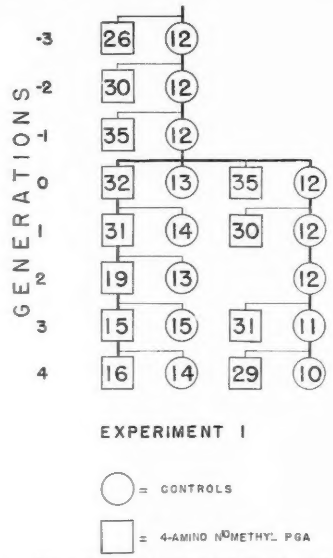

Fig. 1. Genealogy of 4-amino-N^{10}-methyl PGA-resistant strains. The figures in the circles represent the average survival time in days of groups of ten untreated mice; those in the squares the average survival time of groups of ten mice treated with 4-amino-N^{10}-methyl-PGA 3 mg/kg intraperitoneally three times weekly.

Many examples of the development of drug-fast strains in microorganisms under drug treatment *in vitro* and *in vivo* have been noted in the history of chemotherapy (*1*, *4*, *7*). Unpublished work elsewhere has shown a similar drug fastness to develop in cells of tumors of chloroleukemia Ak 1394 in mice treated with benzene (*5*).

The experimental studies undertaken to develop such a drug-resistant subline in mice are herewith reported. Akm mice inoculated with leukemia Ak 4 in from the 21st to the 35th transplanted generation were used in these experiments. Saline suspensions of splenic tissue, which had been obtained from mice dying of leukemia Ak 4 despite continued therapy with 4-amino-N^{10}-methyl-PGA in doses of 3 mg/kg given three times weekly, were inoculated intraperitoneally into 20 Akm mice. Forty-eight hr later these were divided into two groups of ten mice each. One group was considered as a control and received no treatment. The other group was treated with 4-amino-N^{10}-methyl-PGA in doses of 3 mg/kg given intraperitoneally three times weekly until death. The average survival time of treated and control mice was noted and transfer of the line continued through one of the treated mice. The genealogy and differing response to therapy of sublines after repeated passages through treated or untreated mice can be seen in Fig. 1.

In experiment 1, a subline of this lukemia developed complete resistance to 4-amino-N^{10}-methyl-PGA after three

[1] This investigation was supported in part by a research grant from The National Cancer Institute of The National Institutes of Health, United States Public Health Service, and in part by a research grant from The American Cancer Society.

[2] We are indebted to Dr. J. H. Williams of the Lederle Laboratories for our supply of this compound.

passages through treated mice. This can be contrasted with identical generations in which passage of the leukemia was continued through the untreated mice. In these, as would have been expected, the sensitivity of the disease to therapy continued unchanged (Fig. 1). In a second experiment using the same original strain of Ak 4 leukemia, a marked drop in the survival time of the treated mice occurred after the first passage through treated mice. For the next two passages no further increase in resistance was noted, but after the fourth transfer a drug-fast strain developed which showed no significant difference in the survival time of treated and untreated mice. Both groups died approximately 12 days after the inoculation of the leukemia. This subline is now in the ninth transfer generation through treated mice. All continue to be resistant to the usual therapy with 4-amino-N^{10}-methyl-PGA. This procedure has been repeated with a third subline with similar results.

No morphologic differences between the cells of the sensitive and of the resistant sublines of this leukemia have been observed, and sections taken at the time of death from mice inoculated with the normal or the resistant sublines were indistinguishable. Studies are in progress in an attempt to demonstrate biochemical differences between these cells.

It is felt that this demonstration of the ability of a hitherto sensitive leukemic strain to develop resistance to 4-amino-N^{10}-methyl-pteroylglutamic acid may help to explain the eventual failure of this type of therapy in patients with acute leukemia.

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Hemin Synthesis in Spleen Homogenates

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It has been demonstrated by Altman *et al.* (*2*) that the alpha carbon atom of glycine is incorporated in the hemin and globin moieties of the hemoglobin molecule when glycine labeled with C^{14} in the methylene carbon atom is fed to rats. Several instances of hemin synthesis *in vitro* are known. It has thus been shown that hemin synthesis from methylene carbon-labeled glycine takes place in rabbit bone marrow homogenates (*3*). It has also been shown that nucleated avian erythrocytes are capable of hemin synthesis *in vitro* when glycine labeled with N^{15} is added to the incubation mixture (*9*). Since there exists histological evidence of extra-medullary hematopoietic activity in the spleen (*4, 7*), it was thought of interest to test with biochemical methods the possibility of hemin synthesis from labeled glycine in spleen homogenates in the manner previously applied to bone marrow homogenates (*3*).

Rabbit spleens were chosen as the source of the homogenates, spleens from several rabbits having been pooled for each experiment. A spleen homogenate from three rabbit spleens, 8–10 g wet weight in toto, was prepared as follows: The spleens were homogenized in the microcup of the Waring blender with 25 ml of 0.9% NaCl solution. To the resulting homogenate were added 0.15 millimoles of glycine (containing concentrations of $C^{14}H_2NH_2COOH$[2] indicated in Table 1), 0.06 millimoles of sodium acetate, and 1.5 ml of M/2 phosphate buffer pH 7.3. The homogenates were then incubated at 38° C for appropriate periods of time. After addition of 10 mg crystalline hemin as carrier, either hemin or protoporphyrin IX dimethyl ester was isolated, hemin according to Nencki and Zaleski (*8*) and protoporphyrin according to Grinstein (*6*). The protoporphyrin dimethyl ester was recrystallized three times from chloroform and once from pyridine (mp 223–225°). Hemin was recrystallized once as described by Fischer (*5*). The determination of C^{14} activity was carried out with the ionization chamber apparatus of Bale and Masters, as previously described (*2*). The results obtained are shown in Table 1.

TABLE 1

Time of incubation in hr	C^{14} activity of glycine 10^6 disintegrations/min/millimole	C^{14} activity of protoporphyrin IX dimethyl ester 10^4 disintegrations/min/millimole	C_0/C†
3	4.6	16.4	28.0
14½	7.2	48.8	14.8
25	5.3	60.0*	8.8

* Isolated as hemin.
† C_0/C = ratio of C^{14} activity of compound added (C_0) to C^{14} activity of compound isolated (C), i.e., the dilution constant.

One experiment (3-hr incubation) was carried out in a large Warburg vessel permitting the collection of evolved CO_2 in 5*N* NaOH with subsequent isolation as $BaCO_3$. The C^{14} activity of the $BaCO_3$ thus obtained was quite low (4.8×10^2 disintegrations/min/millimole), indicating that only very small amounts of the methylene carbon atom of glycine were converted to CO_2 in spleen homogenates. The C_{16}–C_{18} fatty acids isolated in several cases contained significant C^{14} activities, although the dilution of the radioactivity was somewhat higher than that pre-

[1] This paper is based on work performed under contract with the U. S. Atomic Energy Commission at the University of Rochester Atomic Energy Project, Rochester, New York.

[2] The authors are indebted to Dr. B. M. Tolbert, of the Radiation Laboratories, University of California, for making available the labeled glycine used in these experiments.

viously reported for bone marrow homogenates (*1*). Active protein and nucleic acid synthesis also appeared to take place in these spleen homogenates.

The results reported here indicate that hemin synthesis can be carried out by rabbit spleen homogenates utilizing the methylene carbon atom of glycine as a precursor. Experiments are now in progress to assess the biological significance of these findings.

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Effect of 2,4-Dichlorophenoxyacetic Acid on the Alpha and Beta Amylase Activity in the Stems and Leaves of Red Kidney Bean Plants[1]

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Recent work (*2, 4, 5, 7, 8*) has shown that treatment of plants with 2,4-dichlorophenoxyacetic acid (2,4-D) results in a reduction of carbohydrates and an accumulation of nitrogen. Since minute quantities of 2,4-D produce these marked changes in the chemical composition of the plants, it is indicated that the enzyme system might be involved. The purpose of this communication is to report the effect of 2,4-D on the alpha and beta amylase activity in the stem and leaf tissue of red kidney bean plants.

Seeds of red kidney bean plants were selected for uniformity of size and planted in 4-in. pots in the greenhouse. Each pot contained two plants that were treated when the first trifoliate leaf was expanding. Four replications of 100 plants each were used from which to obtain material of treated and nontreated plants (controls). Application of 2,4-D was made by applying one drop (0.05 ml) of a 1000-ppm solution to the base of the blade of one of the primary leaves. The plants were harvested 6 days after treatment, at the time the stem tissue had proliferated considerably but yet showed no signs of necrosis. The plants were air-dried in the dark and then separated into the various parts. The hypocotyl, first internode, and leaf petioles were grouped together as stem tissue. Enzyme activity was determined separately on the stem and leaf tissue.

[1] Journal Article No. 1066, Michigan Agricultural Experiment Station, East Lansing.

TABLE 1

EFFECT OF 2,4-D ON ALPHA AND BETA AMYLASE ACTIVITY IN STEMS AND LEAVES OF RED KIDNEY BEAN PLANTS*

Enzyme	Replication	Stems non-treated	Stems treated	Leaves non-treated	Leaves treated
Alpha amylase†	1	29.91	4.63	0	0
	2	31.90	4.90	0	0
	3	32.32	5.02	0	0
	4	33.20	5.23	0	0
	avg	31.83	4.95	0	0
Beta amylase‡	1	38.70	21.15	25.87	27.91
	2	33.40	25.99	26.20	26.90
	3	35.60	26.22	27.62	28.34
	4	38.60	22.34	25.62	26.34
	avg	36.58	23.93	26.33	27.37

* Each figure is the average of two determinations of each replication. Results are expressed on a dry weight basis.

† Expressed as the number of grams of soluble starch which under the influence of an excess of beta amylase are dextrinized by 1 g of tissue in 1 hr at 30° C.

‡ Expressed as number of grams of soluble starch converted to maltose by the beta amylase of 1 g of tissue in 1 hr at 30° C.

The alpha and beta amylase were determined according to the method of Kneen and Sandstedt (*1, 3, 6*). The data in Table 1 show that 2,4-D lowers considerably the activity of both the alpha and beta amylase in the stems of bean plants. No activity of alpha amylase was noted in leaves of the treated and nontreated plants. The results also show that treating leaves of the plants with 2,4-D had no effect on the beta amylase activity.

Further work is in progress on the effect of 2,4-D upon enzyme activity in various tissues of the plant.

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NEWS and Notes

Richard P. Feynman, Cornell University physicist, will present twelve lectures, beginning February 6, as the third seminar series in physics at California Institute of Technology, Pasadena. I. I. Rabi and J. Robert Oppenheimer conducted the first two series. Dr. Feynman's subject is "Quantum Electrodynamics and Meson Theories."

Byron J. Olson, senior surgeon at the National Institutes of Health, has been appointed assistant chief of the NIH Laboratory of Infectious Diseases, Bethesda, Maryland.

Earle M. Billings has resigned as secretary of the American Chemical Society's Committee on Professional Training because of ill health. He has held the post since the committee was organized in 1936 to raise the standards of the teaching of chemistry in colleges and universities. The new secretary is **John Howard,** Eastman Kodak Company's business and technical personnel director. The committee has headquarters in Rochester, New York.

Richard E. Vaughan will retire as professor emeritus from the post of extension plant pathologist at the University of Wisconsin on January 31. Dr. Vaughan, who has held the position since 1915, was one of the first extension pathologists in the country.

The 17th annual E. Starr Judd Lecture in surgery will be given by **Henry K. Beecher,** Dorr Professor of Research in Anesthesia, Harvard Medical School, on Thursday evening, February 16, at the University of Minnesota, Minneapolis. Dr. Beecher's subject is "Growth in the Field of Anesthesia: Some Problems in the Control of Pain."

Gordon H. Scott, acting dean of the Wayne University College of Medicine since September 1948, has been named dean of the college. Before coming to Wayne, Dr. Scott was chairman of the Department of Anatomy at the University of Southern California.

Louis Koenig, former chairman of chemistry and chemical engineering at Armour Research Foundation, Chicago, has been appointed to the newly created position of assistant director of research at Stanford Research Institute, Stanford, California. Dr. Koenig will have full administrative charge of institute activities in chemistry, chemical engineering, metallurgy, applied biology, food technology, and pharmacology.

Harvey Fletcher, former director of physical research for the Bell Telephone Laboratories, has been appointed visiting professor of electrical engineering at the Columbia University School of Engineering for the spring session. He will give two new courses, one on elements of acoustical engineering, the other on speech and hearing as applied to communication. Dr. Fletcher retired last October after 33 years with Bell Laboratories.

Eleanor Heist Slifer, assistant professor of zoology at the State University of Iowa, has been granted a years's leave of absence to serve as consultant and adviser for the Anti-Locust Research Center of the United Kingdom Colonial Office. Dr. Slifer will do research on locust physiology, which forms part of the general investigation being conducted at Cambridge and other universities in England. During the year beginning February 1 Dr. Slifer's address will be Department of Zoology, Cambridge University, Cambridge, England.

Grants and Awards

The Benjamin Franklin Medal was awarded to Charles F. Kettering, research consultant of the General Motors Corporation, at a luncheon meeting of the International Benjamin Franklin Society held in New York City on January 21. The gold medal, given for outstanding results in science, was presented to Dr. Kettering by George L. Bliss, president of the society.

The Sarah Mellon Scaife Foundation has awarded two grants totaling $35,000 to the University of Pittsburgh. The Addison H. Gibson Medical Laboratory at the university received $10,000. The laboratory is conducting research in arteriosclerosis and other heart and circulation problems and the use of radioactive isotopes in medicine. The remaining $25,000 will be used for a study of nursing service.

The Institute of Radio Engineers, at its annual meeting in New York City, March 6–9, will present the following awards: *1950 IRE Medal of Honor* to Frederick E. Terman, dean of the School of Engineering, Stanford University, for his contributions to radio and electronics as teacher, author, scientist, and administrator; *Browder J. Thompson Memorial Prize* to Joseph F. Hull, research engineer, and Arthur W. Randals, research physicist, for "High Power Interdigital Magnetrons" done for the U. S. Army Signal Corps; *Harry Diamond Memorial Award* to Andrew V. Haeff, consultant, Naval Research Laboratory, for his work in high frequency radio analysis, the traveling wave tube, and memory storage devices.

Fred L. Soper, director of the Pan American Sanitary Bureau, was awarded the **Theobald Smith Gold Medal** at a recent meeting of the American Society of Tropical Medicine, the American Academy of Tropical Medicine, and the National Malaria Society. The award was presented to Dr. Soper for his work as director of the Brazilian Yellow Fever Service in the eradication of two mosquito vectors, *Anopheles gambiae* and *Aëdes aegypti.*

The 1949 John Jeffries Award, sponsored by the Institute of Aeronautical Sciences, has been presented to A. D. Tuttle, medical director of the United Air Lines. The award, which honors the memory of John Jeffries, who made the first aerial voyage across the English Channel in 1785 with the French balloonist, Blanchard, is given for outstanding contributions to the advancement of aeronautics through medical research.

The 14th annual award of the **Oersted Medal** of the American Association of Physics Teachers will

be made to Orrin H. Smith, professor of physics at De Pauw University, Greencastle, Indiana. Prof. Smith will receive the award for his contributions to the teaching of physics at the annual meeting of the association in New York, February 2–4.

The Stephen Hales Prize has been awarded Robert Emerson, research professor of botany at the University of Illinois, by the American Society of Plant Physiologists in recognition of his work in photosynthesis. Dr. Emerson will deliver the Stephen Hales Lecture at the next meeting of the society.

Visitors to U. S.

Julien R. J. Goens, Laboratoire de Physique, École Royale Militaire, Brussels; **Jacob Ramm,** director, Children's Dental Treatment, Oslo; and **R. R. Warnecke,** technical director, Centre de Recherches de la Compagnie Generale de Telegraphie Sans Fil, Paris, visited the National Bureau of Standards during the week of January 16–20.

Fellowships, Assistantships, and Prizes

The Plant Research Institute and the Botanical Laboratories of the University of Texas are offering the following fellowships and assistantships for the acadamic year 1950–51: four teaching fellowships in the Botanical Laboratories ($800–$1,620); six research fellowships on problems within the Plant Research Institute, with preference given to applicants interested in physiology, genetics, morphology, anatomy, cytology, or ecology ($1,500–$2,400); one postdoctoral fellowship for work on an advanced problem (selected in consultation with the institute staff) within the fields of physiology, experimental morphology, or developmental genetics ($3,000); several graduate and undergraduate teaching and research assistantships in both the laboratories and the institute (approximately $1,000 for nine months); university fellowships to graduate students working toward advanced degrees (ranging up to $1,000 for 9 months).

Complete information concerning these fellowships and assistantships may be obtained from Dr. W. Gordon Whaley, Botanical Laboratories, University of Texas, Austin 12.

The Williams-Waterman Fund of the Research Corporation has made available to the **Institute for Enzyme Research of the University of Wisconsin** two fellowships for training in enzyme chemistry. One of the fellowships is intended for recent graduates with a Ph.D. degree and the other is for a senior investigator. The stipends will range from $3,000 to $4,000. Applications should be sent to Dr. D. E. Green of the Institute for Enzyme Research.

The American Cancer Society is offering a limited number of clinical fellowships for 1950–51. The fellowships are awarded to institutions only, upon application by deans, executive officers, or department heads. Selection of individual recipients of the fellowships is then made by the designated institutions. Fellowships are for a minimum of one year, and may be renewed up to a maximum of three years, with an annual award of $3,600. Training may be either general or specific. Individual recipients must be graduates of Class A medical schools, not over 40 years of age, and have completed one year of postgraduate training, exclusive of internship. Those interested should consult the appropriate authority in the institution of their choice. Institutional applications must be submitted prior to *February 15*, and should be sent to Dr. Brewster S. Miller, Assistant Director, Professional Education Section, American Cancer Society, 47 Beaver Street, New York City.

Lehigh University offers the following graduate fellowships for the 1950–51 academic year: *Dupont Company Fellowships in Mechanical and Metallurgical Engineering*—$1,200 for single fellow, $1,800 for married fellow, preference given to applicants who have already done considerable work toward the doctorate; *George Gowen Hood Fellowship* (supported by the Catherwood Foundation)—$1,500 for work in any field in which the university offers the doctoral degree; *International Nickel Company Fellowship in Metallurgical Engineering*—$1,500; *Francis Mac D. Sinclair Fellowship in Chemistry*—offered in connection with the research program of the National Printing Ink Research Institute for work in the fundamental physical chemistry of systems related to printing ink, $1,200–$1,800; *Westinghouse Fellowship in Mechanical Engineering*—$1,000. All fellowships except Westinghouse are free from tuition fees; the Westinghouse award may be so augmented by the university. Further information is available from Dean Wray H. Congdon, Director of Admissions, Lehigh University, Bethlehem, Pennsylvania.

Two research fellowships in biology and two research assistantships in bacteriology will be awarded for 1950–51 by the University of Delaware. Each will carry a stipend of $1200 for 12 months. Application blanks may be obtained from the chairman of the Graduate Division of the university, and applications should be sent to the chairman of the Department of Biological Sciences not later than *March 1*.

The Institute for the Unity of Science is offering a prize of $300 for the best essay on the theme "The Divorce Between Science and Philosophy: Its Historical Origins, Its Logical Basis, and Proposals for Its Termination." Two additional prizes of $100 each will be given for the next best two essays. The contest is open to college and university students in the U. S. or Canada, as well as to any recipient of a Ph.D. degree obtained since July 1, 1947. Essays must not exceed 10,000 words and must be submitted before *January 1, 1951*. Further information can be obtained from the Institute for the Unity of Science, American Academy of Arts and Sciences, 28 Newbury Street, Boston 16, Massachusetts.

A graduate fellowship in chemical genetics or biochemistry has been established at the California Institute of Technology by the McCallum Foundation, in cooperation with the Nutrition Foundation. This fellowship provides for tuition, living expenses, and research supplies, up to a total of $2,500 per year,

and is renewable for a second year. The recipient will be expected to choose a thesis problem concerned with the question of how ingredients of foodstuffs are built up and utilized in living cells. Applications for the McCallum Fellowship should be made through the Dean of the Graduate Studies, California Institute of Technology, Pasadena 4, California.

Colleges and Universities

An institute on Design of clinical research in psychology, psychiatry, and social work will be presented by the Departments of Psychology and Social Welfare of **the University of California Extension and the University of California at Los Angeles.** James G. Miller, chairman of the Department of Psychology at the University of Chicago, will conduct the institute. Sessions begin on February 6, and will be open to nonstudents. Information concerning the institute is available at the university extension offices at 813 South Hill Street, Los Angeles 14, or at UCLA.

The Institute for Nuclear Chemistry at Upsala University, Sweden, was formally opened on December 8. T. Svedberg, who has retired after more than four decades of teaching at the university, will carry on his investigations at the new institute as professor emeritus. The institute's subterranean cyclotron is nearing completion.

The seventh annual Wayne University lecture series, "Frontiers in Chemistry," will be held on Monday evenings beginning February 27, in Room 101, Science Hall, on the Wayne campus in Detroit. The series is cosponsored by the International Society of the Friends of the Kresge-Hooker Library and Wayne's Department of Chemistry. Speakers are: Arthur C. Cope, Massachusetts Institute of Technology; John R. Johnson, Cornell University; Ralph S. Shriner, State University of Iowa; Carl Niemann, California Institute of Technology; Morris Kharasch, University of Chicago; Charles R. Hauser, Duke University; William G. Young, University of California, Los Angeles; and S. M. McElvain, University of Wisconsin. Additional information may be obtained from Dr. J. Russell Bright, Chairman, Department of Chemistry, Wayne University, Detroit, Michigan.

Industrial Laboratories

Bausch and Lomb Optical Company has elected M. Herbert Eisenhart as chairman of its board of directors. Dr. Eisenhart has been president of the company since 1935. Joseph F. Taylor, vice president and treasurer, was elected to succeed Dr. Eisenhart as president. William W. McQuilkin, who joined the company as counsel in 1938, and has been assistant treasurer since 1947, succeeds Dr. Taylor as treasurer.

Robert T. Connor, vice president of research and development at the Harrower Laboratories, Inc., of Glendale, California, has been appointed technical assistant to the director of the research laboratories of **Smith, Kline and French Laboratories,** Philadelphia.

M. William Amster, of Schering Corporation, Bloomfield, New Jersey, has been made head of the company's Medical Service Department. He succeeds **Norman L. Heminway,** who becomes associate director of the Clinical Research Division.

The Mohave Instrument Company, manufacturers of geological and scientific instruments, changed its name to Stratex Instrument Company on January 1. Offices are located at 1861 Hillhurst Avenue, Los Angeles.

Meetings and Elections

The 17th annual assembly of the American Academy of Orthopaedic Surgeons will meet at the Waldorf Astoria Hotel in New York City on February 11–16. The first day will be devoted to an audio-visual education program, including a number of movies demonstrating various bone and joint operations and allied subjects. On February 12 and 13 courses in bone surgery will be presented.

Plans are being made for **an international colloquium on rheological problems in biology,** to be held in July, 1950, in Scandinavia. Papers will be presented in such fields as the circulation of blood, the mechanical properties of muscle, the movements of sap in plants, and the rheological behavior of protoplasm. The colloquium is being arranged under the auspices of the Joint Committee on Rheology of the International Council of Scientific Unions by an organizing subcommittee consisting of H. Eyring (Utah), A. Frey-Wyssling (Zurich), G. van Iterson (Delft), and P. Eggleton (Edinburgh). Further information may be obtained from Dr. Eggleton, Department of Physiology, University of Edinburgh, Edinburgh 8.

An international symposium on chloromycetin, with special regard to typhoid fever and brucellosis, will be held in Milan during the second Italian Congress on Antibiotics, June 3–5. Research workers and physicians from Europe and the U. S. will participate. Additional information may be obtained from the Italian Center of Studies on Antibiotics, Via Francesco Sforza 38, Milan.

A conference on the properties of semiconducting materials will be held at the University of Reading, July 10–15, under the auspices of the International Union of Physics in cooperation with the Royal Society and assisted by Unesco. The conductive properties of nonmetallic solids, photoconduction, barrier-layer rectifiers, crystal triodes, and related theoretical issues are among the subjects to be presented by leading research workers from Czechoslovakia, France, the Netherlands, Sweden, Switzerland, Great Britain, and the U. S. who have accepted invitations to contribute papers. The conference will be organized by N. F. Mott and R. W. Ditchburn, British physicists. Proceedings will be published in book form. Further information can be had by writing to Dr. H. K. Henisch, Department of Physics, University of Reading, Reading, England.

The American Physical Society will hold its 298th meeting at Oak Ridge, Tennessee, March 16–18, in conjunction with the society's Division of Solid State Physics' annual meeting. Further information may be obtained from Karl K. Darrow, secretary, American Physical Society, Columbia University, New York City 27.

The Office of Naval Research Advisory Panel on Microbiology will hold its spring meeting in Washington, D. C. April 14–15. Proposals for ONR sponsorship of basic research in the field of microbiology received before *March 15* will be reviewed at that time. Roger D. Reid is head of the Microbiology Branch, which directs activities in bacteriology, virology, immunology, parasitology, mycology, and pathology.

The following officers have been elected for 1950 by the **Society of Systematic Zoology**: president, Lee R. Dice, Laboratory of Vertebrate Biology, University of Michigan; president elect, Carl L. Hubbs, Scripps Institution of Oceanography, La Jolla, California; and secretary-treasurer, Richard E. Blackwelder, of the U. S. National Museum.

The Torrey Botanical Club elected the following officers for 1950 at its annual meeting held January 17: president, Harold H. Clum, Hunter College; first vice president, A. E. Hitchcock, Boyce Thompson Institute for Plant Research; second vice president, L. M. Black, Brooklyn Botanic Garden; treasurer, Elva Lawton, Hunter College.

Deaths

Caleb Lothrop Smith, professor of analytical and inorganic chemistry at the State University of Iowa, Iowa City, and head of that division, died on December 26 at the age of 43 after a long illness. He had been on the teaching faculty of the university since 1931 with the exception of two years spent at the metallurgical laboratory of the University of Chicago and at the Clinton Engineering Works of Tennessee Eastman Corporation at Oak Ridge during World War II.

Charles S. Parker, mycologist and professor emeritus of botany, who retired as head of the Department of Botany at Howard University June, 1947, died January 10 in Seattle, Washington, at the age of 68. Dr. Parker is best known for his monograph on the North American genera of Hypholoma.

Charles J. Moore, professor emeritus of chemistry at Hunter College, died at his home in Jacksonville, Florida at the age of 74. Dr. Moore was professor of chemistry and head of the Department at Hunter for 24 years until his retirement in June, 1945.

A new edition of the **U. S. National Commission for Unesco publication** "Study Abroad," Volume II (see *Science*, 109, p. 218) is now available and brings up to date the list of fellowships, scholarships, and grants for study in 53 nations and 23 territories. Copies are available from the Columbia University Press, 2960 Broadway, New York, at $1.25.

Black Rock Forest, Cornwall-on-Hudson, New York, a private forest experiment station specializing in silvicultural research, has been bequeathed by the will of the late owner, Ernest G. Stillman, to Harvard University. A substantial endowment is included in the bequest. It is expected that research will continue under the aegis of the Harvard Forest School. Henry H. Tryon has retired as director of the forest.

The National Chemical Laboratory of India was officially opened by the Prime Minister of India, Pandit Nehru, on January 3. It is the seventh national laboratory to be completed of the eleven planned by India's Council of Scientific and Industrial Research.

The building, begun in April, 1947, is of western design and magnificent proportions and is set in a natural amphitheatre of hills about four miles from Poona. It is equipped for scientific research in chemistry, in both pure and applied fields, and when completely staffed will operate through nine departments—organic chemistry, biochemistry, chemical engineering, plastics and high polymers, survey and information, inorganic chemistry, physical chemistry, administration and standardization of chemicals, development of Bhilawan and Cashew products. It will thus provide means for effective cooperation between scientific research and industrial production.

The problem of collecting the right personnel for staffing the laboratory is gradually being solved by the director, J. W. McBain, former chemistry professor at Stanford University, whose unceasing work since his arrival in October, 1949, is largely responsible for the advanced stage which the laboratory has reached. Several of the nine departments are already operating and about 76 of the staff, which will ultimately number some 150 scientists, have been appointed.

The opening ceremonies were presided over by the Governor of Bombay. Others who took part were Syama Prasad Mookerjee, Minister of Industry and Supply, and vice president of the council; S. S. Bhatnagar, director, Scientific and Industrial Research; and four Nobel laureates, Sir Robert Robinson, A. H. Compton, Irene Joliot-Curie, and Sir C. V. Raman. After the opening, the laboratory was inspected by Pandit Nehru, Dr. McBain, and a large number of scientists, including many from overseas. About 5,000 attended the ceremony.

Recently Received—

International Control of Atomic Energy and the Prohibition of Atomic Weapons. Recommendations of the United Nations Atomic Energy Commission. U. S. Department of State. Publ. 3646. U. S. GPO, Washington 25, D. C.

Water Temperature Records from California's Central Valley, 1939–48. Special Scientific Report, Fisheries No. 2, Fish and Wildlife Service, U. S. Department of the Interior, Washington, D. C.

Sea Turtles and the Turtle Industry of the West Indies, Florida and the Gulf of Mexico, with Annotated Bibliography. Robert M. Ingle and F. G. Walton Smith. Marine Laboratory, University of Miami, Coral Gables, Fla.

Proceedings of the Gulf and Caribbean Fisheries Institute, August, 1948. Marine Laboratory, University of Miami, Coral Gables, Fla.

High-Frequency Voltage Measurement. Myron C. Selby. Circ. 481, National Bureau of Standards. U. S. GPO, Washington 25, D. C. 20 cents.

Personnel Placement

CHARGES and REQUIREMENTS for "PERSONNEL PLACEMENT" Ads

1. Rate: 15¢ per word, minimum charge $3.00 for each insertion. If desired, a "Box Number" will be supplied, so that replies can be directed to SCIENCE for immediate forwarding. Such service counts as 8 words (e.g., a 25-word ad, plus a "Box Number", equals 33 words). All ads will be set in regular, uniform style, without display; the first word, only, in bold face type.

For *display* ads, using type larger or of a different style than the uniform settings, enclosed with separate border rules, the rate is $16.00 per inch; no extra charge for "Box Numbers".

2. Advance Payment: All Personnel Placement ads, *classified* or *display*, must be accompanied by correct remittance, made payable to SCIENCE. Insertion can be made until payment is received.

3. Closing Date: Advertisements must be received by SCIENCE, 1515 Mass. Ave., N.W., Washington 5, D. C., together with advance remittance, positively not later than 14 days preceding date of publication (Friday of every week).

POSITIONS WANTED

Biochemist: Ph.D. Teaching and research at Eastern Medical School. Federal research on antibiotics. Many publications. Desires teaching or research position. Box 23, SCIENCE. 2/10

Chemist: Ph.D.; six years, biochemist, research institution, duties principally enzyme research; five years, assistant professor of clinical metabolism; since 1942, research director in industry; for further information, please write Burneice Larson, Medical Bureau, Palmolive Building, Chicago. X

Physicist (Ph.D.), experience in research, teaching, administration, desires science-administration position in industry or university which requires both scientific training and executive ability. Box 19, SCIENCE. X

Physicist: M.A. Fifteen years laboratory experience. Desires applied electronics or University connection leading to Ph.D. Box 26, SCIENCE. 2/10

Physiologist, Ph.D.: Experienced, competent in teaching and research. Seeks responsible position, academic or hospital. Box 25, SCIENCE. X

Zoologist: Ph.D. Male. Desires position for summer session at Biological Station, University, or Teachers College. Assistant professor in Big 10 university. Several years experience teaching aquatic biology, field and invertebrate zoology. Box 21, SCIENCE. X

Zoologist: Ph.D. Desires teaching position, West. General zoology; comparative, mammalian, and general physiology; vertebrate, invertebrate anatomy and embryology; ornithology. Available, September, 1950. Box 27, SCIENCE. X

41 REPLIES received from ONE classified ad in SCIENCE . . . . YOUR ad here will get RESULTS **!**

AVOID DELAY . . . . ***Cash in Advance payment*** MUST be enclosed with ALL classified ads.
(See "Charges and Requirements" above.)

POSITIONS OPEN

Bacterial Biochemistry: Young Ph.D.'s interested in research under pending grant beginning April 1950; location east; please register, giving background. Box 24, SCIENCE. X

Pharmacologist or Physiologist: Recent Ph.D. or experienced M.S. as assistant to pharmacologist for pharmacodynamic research in growing pharmaceutical company in Metropolitan New York. Give details in first letter. All replies confidential. Box 18, SCIENCE. 2/24

Personnel Placement

POSITIONS OPEN

Positions Open:
(a) **Director of professional education;** duties: responsibilities of conducting training program in psychiatry, medicine, psychology, social work; physician or Ph.D. in psychology, or education; midwestern teaching center. (b) **Assistant professor** or instructor, physiology department distinguished for its research and graduate program; eastern university. (c) **Pharmacologist** capable of screening tests on various types of synthetics; should be familiar with pharmacological apparatus and procedures; pharmaceutical company; Midwest. (d) **Biochemist;** Ph.D. or M.D. to head division of biochemistry, large teaching hospital; opportunity faculty appointment; $6500–$8500. (e) **Pharmacologist;** medical degree desirable; duties consist of establishing and administering clinical research programs on new products; Pacific Coast. (f) **Immunologist:** Ph.D. or M.D.; senior post, research department, pharmaceutical company; duties primarily research on animal evaluation of new substances for pharmaceuticals. (g) **Physicist;** group clinic specializing in radiology; university medical center; West. S2-1 Burneice Larson, Medical Bureau, Palmolive Building, Chicago. X

Scientists: Salaried positions, $3,600 to $25,000. This confidential service for outstanding men who desire a change of connection, will develop and conduct preliminary negotiations without risk to present position. Send name and address for details. Tomsett Associates, 1205 Berger Building, Pittsburgh 19, Pa. X

Wanted: Plant Pathologist. Teaching position (part-time research). Opportunity for advancement. Rank and salary contingent on training and experience. Inquire immediately, Position now open. Box 22, SCIENCE. 2/17

Writer: Psychological, psychiatric, or mental health background. Must be experienced writer, for both professional and lay audience. Need not be M.D. Location Southwest. Give complete details, samples, photograph, and salary expected. Box 17, SCIENCE. 2/10

The Market Place

BOOKS

OUT-OF-PRINT and HARD-TO-FIND books supplied. All subjects, all languages. Also incomplete sets completed, genealogies and town histories, all magazine back numbers, etc. Send us your list of book-wants—no obligation. We report quickly. Lowest prices.

(We also supply all current books at bookstore prices postpaid)

AMERICAN LIBRARY SERVICE
117 West 48th St., Dept. 222, New York 19, N. Y.
P.S. We also buy books and magazines. Send us your list.

Your sets and files of scientific journals
are needed by our library and institutional customers. Please send us lists and description of periodical files you are willing to sell at high market prices. J. S. CANNER AND COMPANY, 909 Boylston Street, Boston 15. Massachusetts. tf

WANTED TO PURCHASE:
SCIENTIFIC PERIODICALS
Sets and runs, foreign and domestic
SCIENTIFIC BOOKS
Entire libraries and smaller collections
WALTER J. JOHNSON
125 East 23rd Street, New York 10, N. Y.

Send us your Lists of tf
SCIENTIFIC BOOKS AND PERIODICALS
which you have for sale.
Complete libraries; sets and runs; and single titles are wanted.
Also please send us your want lists.
STECHERT-HAFNER, INC., 31 East 10th Street, New York 3.

MEDICAL AND SCIENTIFIC BOOKS. Rare, Out-of-Print. Lists available. Current books supplied. Books purchased. CAMBRIDGE BOOK HOUSE, 320 East 69th Street, N. Y. 21. 2/24

The Market Place

CHARGES and REQUIREMENTS for "MARKET PLACE" Ads

1. Rate: 20¢ per word for *classified* ads, minimum charge $5.00 for each insertion. Such ads are set in uniform style, without display; the first word, only, in bold face type.
For *display* ads, using type larger or of a different style than the uniform classified settings, and entirely enclosed with separate rules, rates are as follows:

Single insertion	$16.00 per inch
7 times in 1 year	14.50 per inch
13 times in 1 year	13.00 per inch
26 times in 1 year	11.50 per inch
52 times in 1 year	10.00 per inch

2. Payment: For all *classified* ads, payment in advance is required, before insertion can be made. Such advance remittances should be made payable to SCIENCE, and forwarded with advertising "copy" instructions.
For *display* advertisers, monthly invoices will be sent on a charge account basis—providing satisfactory credit is established.

3. Closing Date: Classified advertisements must be received by SCIENCE, 1515 Massachusetts Avenue, N.W., Washington 5, D. C., together with advance remittance, positively not later than 14 days preceding date of publication (Friday of every week).
For proof service on display ads complete "copy" instructions must reach the publication offices of SCIENCE, 1515 Massachusetts Avenue, N.W., Washington 5, D. C., not later than 4 weeks preceding date of publication.

LANGUAGES

PROFESSIONAL SERVICES

The Market Place

SUPPLIES AND EQUIPMENT

(The Market Place is continued on page 16)

The Market Place

SUPPLIES AND EQUIPMENT

NEW SPENCER No. 735 LAMP

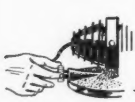
Here is the illuminator for advanced microscopy you knew was bound to come . . . with convenient precise controls for critical adjustment . . . with essential optical and mechanical qualities to complement a fine microscope.

COOLER OPERATION. Sturdy die-cast housing dissipates heat.

CRITICAL FOCUSING FROM EITHER SIDE. Rack & pinion movement.

NO TRANSFORMER. Lamp operates from 110 volt outlet.

PRECISION REFLECTOR ADJUSTMENT. So quick, simple, and accurate.

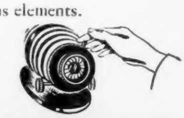


RAPID BULB CHANGE. Lamphouse separates. Hinged lamp chimney opens to reveal bulb and reflector.

PRECISE TILTING. Screw adjustment maintains any angle.

QUALITY OPTICAL SYSTEM. Two plano-convex lens elements.

IRIS DIAPHRAGM. Knurled ring control.



FILTER HOLDER. Choice of single or multiple holder.

Correct illumination is essential for the best results from any microscope objective, eyepiece and condenser. Your instrument deserves the Spencer No. 735. For further details write Dept. B1

American Optical
COMPANY

INSTRUMENT DIVISION • BUFFALO 15, NEW YORK